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(21) International Application Number: PCT/EP96/01881 (22) International Filing Date: 2 May 1996 (02.05.96) (30) Priority Data: 9508989.2 3 May 1995 (03.05.95) GB 9523655.0 18 November 1995 (18.11.95) GB (71) Applicants (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19103 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): BAX, Richard, Peregrine [GB/GB]; SmithKline Beecham Pharmaceuticals, Third Avenue, Harlow, Essex CM19 5AW (GB). RAMSEY, Mike, Gale [US/US]; SmithKline Beecham Pharmaceuticals, Bristol Industrial Park, Weaver Pike, Bristol, TN 37620 (US). (74) Agent: THOMPSON, Clive, Beresford; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOSITION COMPRISING AMOXYCILLIN AND CLAVULANIC ACID			
(57) Abstract Paediatric aqueous liquid suspension formulations comprising amoxycillin trihydrate and potassium clavulanate in a ratio of from 6:1 to 8:1 are provided for use in a BID dosage regimen for treating bacterial infection.			

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Composition comprising Amoxycillin and Clavulanic acid

This invention relates to a method of treating paediatric bacterial infections using a combination of the antibiotic amoxycillin and the beta-lactamase inhibitor
5 potassium clavulanate, to pharmaceutical formulations for use in such method and to methods for the manufacture of such formulations.

The combination of the antibiotic amoxycillin, as amoxycillin trihydrate, and potassium clavulanate, is a well known and widely used oral medicament for bacterial infections, marketed by SmithKline Beecham in many countries under the trade mark
10 Augmentin.

Regulatory approval has been obtained, for instance in the UK and US, for tablets containing amoxycillin (250mg) and potassium clavulanate (125mg) (ratio 2:1), in a three times daily dosing schedule (tid), so that the daily dose of amoxycillin and potassium clavulanate is 750mg and 375mg respectively (the weights being
15 expressed as the free parent acids amoxycillin and clavulanic acid, this manner of expression being used throughout). In severe infections, the ratio is changed to 4:1, so that the daily doses of amoxycillin and potassium clavulanate are 1500mg and 375mg respectively. In other countries such as Italy and Spain, tablets containing amoxycillin (875mg) and potassium clavulanate (125mg) (ratio 7:1) are approved for
20 twice daily dosing (bid). In France, sachets comprising amoxycillin (1000mg) and potassium clavulanate (125mg) (ratio 8:1) are marketed, for reconstitution with water prior to use, as an individual dosage for adults.

For children, it is preferred to provide the combination as a powder which is reconstituted prior to use as a liquid aqueous suspension. The usual recommended
25 daily dosage is 20/5mg/kg/day (UK and USA) or 30/7.5mg/kg/day (Continental Europe) amoxycillin/potassium clavulanate (ratio 4:1), in divided doses every eight hours. For more severe infections such as otitis media, sinusitis and lower respiratory tract infections, the recommended dose is 40/10mg/kg/day (UK and USA) or 60/15mg/kg/day (Continental Europe), in three divided doses. For
30 convenience, the powders are provided in amounts which are made up into a range of volumes of suspension so that a small volume, typically about 5ml, contains a unit dosage. In other countries such as Italy, approval has also been given for using the higher strength paediatric formulation on a twice a day (bid) dosing schedule.

Although it is recognised to be more convenient to be able to recommend a
35 bid dosing schedule for paediatric formulations, to avoid having to give medicine

during the middle of the day when the child may be at school, not all drug substances have pharmacokinetics which are compatible with such a regimen.

In addition, gastric intolerance, manifested in symptoms such as loose stools, is perceived in some countries to be a side effect associated with the use of amoxycillin/potassium clavulanate in the present tid dosage regimes. Accordingly, any measures, such as revised dosage regimes, which can mitigate this would be advantageous.

The present invention therefore provides a method of treating bacterial infections in paediatric patients which method comprises administering to a patient in need thereof, preferably as a liquid aqueous suspension, amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of between 6:1 and 8:1, preferably about 6.5:1 to 7.5:1, more preferably about 7:1 (the weights being expressed as the free parent acids amoxycillin and clavulanic acid), such administration being twice daily (bid) and at a dosage of between 15 and 80mg/kg/day, preferably 20 and 75mg/kg/day, more preferably 20 and 70mg/kg/day, suitably 40 and 70mg/kg/day, of amoxycillin and *pro rata* amounts of clavulanic acid.

The term 'paediatric' as used herein means children in the age range from 0 to about 12 years.

The method is suitable for all infections for which the combination of amoxycillin trihydrate and potassium clavulanate is normally prescribed, for instance infections of the upper and lower respiratory tract, urinary tract, skin and skin structures, for example *otitis media*.

Suitably the twice daily (bid) administration is at 12 hour intervals, although a greater or lesser interval between administrations may be used.

Representative daily amounts of amoxycillin/potassium clavulanate include 25/3.6, 35/5, 45/6.4 and 70/10±10%mg/kg/day.

In a further aspect, the present invention provides for pharmaceutical compositions for use in the aforementioned method of treatment, these compositions being distinguishable over previously available compositions on account of the different ratio of amoxycillin trihydrate:potassium clavulanate used and the differing amounts of amoxycillin trihydrate and potassium clavulanate per unit dose, to achieve the higher daily dosage regime.

The invention therefore provides a pharmaceutical formulation suitable for paediatric oral bid administration, comprising amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of between 6:1 and 8:1, preferably about 6.5:1 to 7.5:1, more preferably about 7:1 (the weights being expressed as the free parent acids amoxycillin and clavulanic acid), and in quantities such as to provide between between 15 and 80mg/kg/day, preferably 20 and 75mg/kg/day, more

preferably 20 and 70mg/kg/day, suitably 40 and 70mg/kg/day, of amoxycillin and *pro rata* amounts of clavulanic acid.

Formulations according to the present invention are preferably provided in the form of a dry powder or granule formulation for reconstitution into an aqueous suspension with water or other suitable aqueous media, shortly before administration. The present invention covers such dry powder and granule formulations as well as liquid aqueous preparations.

Such dry formulations may be provided in a substantially air-tight container such as a bottle or sachet, and this container may suitably include a desiccant to protect the potassium clavulanate from degradation by atmospheric water vapour. Potassium clavulanate is highly moisture sensitive, and the formulations of this invention should be made under conditions of relative humidity (RH) as low as possible, preferably 30% RH or less.

The formulation of this invention is provided for bid administration, which ideally may comprise two administrations at 12 hour dosage intervals, although a greater or lesser interval between administrations may be used.

Suitably, formulations according to the present invention are provided in amounts such that the liquid aqueous suspension contains in a convenient volume, typically within the range 2 to 10ml, preferably about 5ml, of suspension, a unit dosage of amoxycillin and potassium clavulanate. The volume may be measured by any conventional measuring device such as a spoon, syringe or graduated measuring cup. Unit dosages typically lie within the range 50 to 800mg of amoxycillin plus *pro rata* amounts of potassium clavulanate. It will be appreciated that the appropriate unit dosage will be at the discretion of the physician and will depend *inter alia* upon the age and weight of the patient and the nature and severity of the infection to be treated.

It is found to be convenient to provide paediatric formulations in a lower (for mild-moderate infections) and a higher strength (for severe infections). The suitable formulations, when made up as aqueous liquid suspensions, will contain from 100 to 400mg, or 200 to 800mg amoxycillin per 5ml of suspension plus *pro rata* amounts of potassium clavulanate. Representative examples include:

amoxycillin	potassium clavulanate
200	28.5/5ml suspension
400	57;

within a tolerance of $\pm 10\%$.

Accordingly, in a further aspect, the present invention provides a pharmaceutical formulation adapted for reconstitution as a liquid aqueous suspension comprising amoxycillin trihydrate and potassium clavulanate and which, when reconstituted, comprises amoxycillin in an amount $200 \pm 10\%$ and clavulanic acid in an

amount $28.5 \pm 10\%$ or amoxycillin in an amount $400 \pm 10\%$ and clavulanic acid in an amount $57 \pm 10\%$ mg/5ml of liquid aqueous suspension.

In a representative example, for a unit dosages of 5ml, the suspension is made up to a total volume of 100ml. It will however be appreciated that a range of total
5 volumes may be used, to adjust the amount in a unit dose to an amount appropriate for the individual patient. It will be appreciated that it may also be convenient to provide a higher strength formulation to a patient with a larger body weight, so that the unit volume is kept reasonable.

The formulation of this invention will normally comprise, in addition to its
10 active materials amoxycillin trihydrate and potassium clavulanate, excipients which are standard in the field of paediatric pharmaceutical oral suspensions. These will be used in generally standard proportions, and at generally standard particle sizes and grades etc.. Such excipients may comprise suspending aids, glidants (to aid filling), diluents, bulking agent, flavours, sweeteners, stabilisers, and, in the case of dry
15 formulations for make-up to an aqueous suspension, an edible desiccant to assist preservation of the potassium clavulanate against hydrolysis by atmospheric moisture on storage. Potassium clavulanate is normally supplied in admixture with silicon dioxide as diluent. Suitable excipients for use include xanthan gum (suspension aid), colloidal silica (glidant), succinic acid (stabiliser), aspartame (sweetener),
20 hydroxypropylmethylcellulose (suspension aid) and silicon dioxide (desiccant, diluent for potassium clavulanate and bulking agent. Flavours may comprise common flavours such as orange, banana, raspberry and golden syrup, or mixtures thereof, to suit local requirements.

Mannitol is often used in pharmaceutical formulations as an excipient. It is
25 however recognised to have, at least at certain levels, a diuretic effect. It has found to be advantageous to avoid the use of excessive amounts of mannitol in formulations comprising amoxycillin/potassium clavulanate, as it is thought that this may be associated with reduced levels of gastric irritancy. Accordingly, the present invention provides for a pharmaceutical formulation as hereinbefore defined and which is
30 substantially mannitol-free.

Generally the proportion of active materials amoxycillin trihydrate and potassium clavulanate in a dry formulation for make-up with aqueous media into a suspension formulation of the invention may be around 35-60, e.g. 35-50 wt%.

The formulation of the invention may be manufactured using techniques
35 which are generally conventional in the field of manufacture of paediatric suspension formulations and manufacture of dry formulations for reconstitution into such suspensions. For example a suitable technique is that of mixing dry powdered or granulated ingredients for loading into a suitable container.

The present invention therefore provides a process for manufacture of a formulation as described above.

The invention also provides for the use of amoxycillin trihydrate and potassium clavulanate as described above in the manufacture of a medicament which is provided for paediatric oral BID administration for use in the treatment of bacterial infections.

The invention will now be described by way of non-limiting example only.

Example 1

Two formulations of this invention having a composition as listed below were prepared using conventional techniques as dry powder mixtures. The proportions of ingredients are expressed as mg/5ml dose of reconstituted aqueous suspension:

Ingredient	mg/5ml	mg/5ml
amoxycillin trihydrate*	408.0	204.0
potassium clavulanate*	61.56	30.78
xanthan gum	12.5	12.5
colloidal silica	25.0	25.0
succinic acid	0.84	0.84
orange flavour	26.25	26.25
golden syrup flavour	23.75	23.75
aspartame	12.50	12.50
hydroxypropylmethylcellulose	79.65	79.65
silicon dioxide	to 885.5	to 537.5

* expressed as free acid equivalent.

The above two formulations were manufactured in 100 kg batches.

Clinical Trial - A

In a multicentre randomized trial, the safety and efficacy in the treatment of acute Otitis Media in children of formulations according to the present invention and comprising amoxycillin/potassium clavulanate in a ratio of 7:1, at a level of 45/6.4 mg/kg/day (ratio 7:1) and in divided doses q12h (BID) were compared with a currently approved US formulation comprising amoxycillin/potassium clavulanate acid in divided doses q 8h (TID). 287 children received the BID regimen for 10 days and 288 children received the TID regimen for 10 days. The formulations

according to the present invention were mannitol-free whilst the currently approved US formulation contained mannitol.

The BID regimen was shown to be as safe as the TID regimen. Standard diary cards were used to assess the incidence of incidence of protocol-defined diarrhoea (i.e. 3 or more watery stools in one day, or 2 watery stools per day for two consecutive days. This was found to be significantly lower for the BID regimen (7.9%) when compared with the TID regimen (22.2%) [95% CI: (-20.5%, -8.1%)]. Similar trends were observed for withdrawals due to diarrhoea (2.8% and 7.6% respectively; $p = 0.009$), confirming improved patient tolerance compared with the current regimen.

The per protocol clinical success rates at the end of therapy (days 12 to 14) were equivalent for the BID regimen (86.5%) and the TID regimen (78.88%). Similar trends in efficacy were noted at follow-up (days 32 to 38).

Formulations used

Ingredient	bid mg/5ml	bid mg/5ml	tid mg/5ml	tid mg/5ml
amoxycillin trihydrate*	408.0	204.0	130.00	260.00
potassium clavulanate*	61.56	30.78	35.00	70.00
xanthan gum	12.5	12.5	15.00	15.00
sodium saccharin			4.00	4.00
colloidal silica	25.0	25.0	25.00	25.00
succinnic acid	0.84	0.84	0.85	0.85
banana flavour			20.00	
orange flavour	26.25	26.25		23.00
golden syrup flavour	23.75	23.75		
aspartame	12.50	12.50		
hydroxypropylmethylcellulose	79.65	79.65		
silicon dioxide	to 885.5	to 537.5	82.30	39.70
mannitol			to 900.00	to 1200.00

* expressed as free acid equivalent.

Clinical trial - B

In a multicentre randomized trial, the safety and efficacy in the treatment of acute Otitis Media in children of formulations according to the present invention and

- comprising amoxycillin/potassium clavulanate in a ratio of 7:1, at a level of 70/10mg/kg/day (ratio 7:1) and in two divided doses (BID) were compared with a currently approved European formulation comprising amoxycillin/potassium clavulanate in a ratio 4:1 administered at a level of 60/15mg/kg/day
- 5 amoxycillin/potassium clavulanate acid in three divided doses (TID). Children aged from 2-12 years were randomised to 10 days treatment, with 231 children receiving the BID regimen and 232 children receiving the TID regimen.

- 10 The BID regimen was shown to be as safe as the TID regimen. Standard diary cards were used to assess the incidence of protocol-defined diarrhoea (i.e. 3 or more watery stools in one day, or 2 watery stools per day for two consecutive days). The overall incidence was found to be low, with a lower incidence in the BID group (6.7%) than in the TID group (10.3%) although this was not statistically significant [difference - 3.6%; 95% CI (-8.72%, 1.58%)].

- 15 Clinical success rates at the end of therapy were 91.8% for the BID regimen and 90.5% for the TID regimen [difference 1.3%.; 95% CI (-3.92%, 6.43%)] and at follow-up were 80.1% for the BID group and 77.6% for the TID group [difference 2.5%; 95% CI (-4.94%, 9.94%)].

- 20 More patients in the BID group (81.3%) than in the TID group (72.8%) had at least 80% compliance over a 7-10 day treatment period [difference 10.3%; 95% CI (2.78%, 17.76%)].

Formulations used

Ingredient	bid formulation	tid formulation
	mg/5ml	mg/5ml
amoxicillin trihydrate*	400.0	250.00
potassium clavulanate*	59.85	65.63
xanthan gum	12.50	12.50
colloidal silica	25.00	25.00
succinic acid	0.84	0.84
orange flavour	26.25	26.25
raspberry flavour		22.50
golden syrup flavour	23.75	23.75
aspartame	12.50	12.50
hydroxypropylmethylcellulose	79.65	150.00
silicon dioxide	to 885.5	125.00

* expressed as free acid equivalent.

Claims

1. The use of amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of between 6:1 and 8:1 (the weights being expressed as the free parent acids amoxycillin and clavulanic acid), in the manufacture of a medicament for treating bacterial infections in paediatric patients which medicament is administered twice daily (bid), at a dosage of between 15 and 80mg/kg/day of amoxycillin and *pro rata* amounts of clavulanic acid.
2. A use as claimed in claim 1 in which the dosage is between 20 and 75mg/kg/day of amoxycillin.
3. A use as claimed in claim 1 in which the dosage is between 20 and 70mg/kg/day of amoxycillin.
4. A use as claimed in claim 1 in which the dosage is between 40 and 70mg/kg/day of amoxycillin.
5. A use as claimed in any one of claims 1 to 4 in which the weight ratio is from about 6.5:1 to 7.5:1.
6. A use as claimed in any one of claims 1 to 5 in which the weight ratio is about 7:1.
7. A use as claimed in any one of claims 1 to 6 in which the dosage regimen is $70 \pm 10\%$ mg/kg/day amoxycillin in combination with $10 \pm 10\%$ mg/kg/day clavulanic acid.
8. A use as claimed in any one of claims 1 to 6 in which the dosage regimen is $45 \pm 10\%$ mg/kg/day amoxycillin in combination with $6.4 \pm 10\%$ mg/kg/day clavulanic acid.
9. A use as claimed in any one of claims 1 to 6 in which the dosage regimen is $35 \pm 10\%$ mg/kg/day amoxycillin in combination with $5 \pm 10\%$ mg/kg/day clavulanic acid.
10. A use as claimed in any one of claims 1 to 6 in which the dosage regimen is $25 \pm 10\%$ mg/kg/day amoxycillin in combination with $3.6 \pm 10\%$ mg/kg/day clavulanic acid.

11. A use as claimed in any one of claims 1 to 10 in which the formulation is provided as a liquid aqueous suspension.
12. A pharmaceutical formulation adapted for paediatric oral bid administration, comprising amoxycillin trihydrate and potassium clavulanate in combination, in a weight ratio of between 6:1 and 8:1 (the weights being expressed as the free parent acids amoxycillin and clavulanic acid), and which, when reconstituted, comprises amoxycillin in an amount of from 150 to 450mg/5ml of liquid aqueous suspension and clavulanic acid in an amount of from 25 to 75mg/5ml of liquid aqueous suspension.
13. A formulation as claimed in claim 12 in which the weight ratio is between 6.5:1 and 7.5:1.
14. A formulation as claimed in claim 12 in which the weight ratio is between about 7:1.
15. A formulation as claimed in any one of claims 12 to 14 in the form of a dry powder or a granule formulation for reconstitution into a suspension with water or other suitable aqueous media to form a suspension formulation.
16. A formulation as claimed in any one of claims 12 to 14 in the form of a liquid aqueous preparation.
17. A formulation as claimed in any one of claims 12 to 16 provided for administration at a dosage of from 15 to 80 mg/kg/day of amoxycillin.
18. A formulation as claimed in claim 17 provided for administration at a dosage of from 20 to 75 mg/kg/day of amoxycillin.
19. A formulation as claimed in claim 17 provided for administration at a dosage of from 20 to 70 mg/kg/day of amoxycillin.
20. A formulation as claimed in claim 17 provided for administration at a dosage of from 40 to 70 mg/kg/day of amoxycillin.
21. A formulation as claimed in claim 17 provided for administration at a dosage of $45 \pm 10\%$ mg/kg/day amoxycillin and $6.4 \pm 10\%$ mg/kg/day clavulanic acid.

22. A formulation as claimed in claim 17 provided for administration at a dosage of $70 \pm 10\%$ mg/kg/day amoxycillin and $10 \pm 10\%$ mg/kg/day clavulanic acid.
23. A formulation as claimed in claim 17 provided for administration at a dosage of $35 \pm 10\%$ mg/kg/day amoxycillin and $5 \pm 10\%$ mg/kg/day clavulanic acid.
24. A formulation as claimed in claim 17 provided for administration at a dosage of $25 \pm 10\%$ mg/kg/day amoxycillin and $3.6 \pm 10\%$ mg/kg/day clavulanic acid.
25. A formulation as claimed in any one of claims 12 to 24 provided for administration in unit doses of quantities of amoxycillin and clavulanic acid corresponding to amoxycillin : clavulanic acid ratios of $200 \pm 10\%$: $28.5 \pm 10\%$, and $400 \pm 10\%$: $57 \pm 10\%$ mg/5ml.
26. A formulation as claimed in any one of claims 12 to 25 in which the proportion of amoxycillin and clavulanic acid is from 35-60 wt%, in a dry formulation for make-up with aqueous media into a suspension formulation.
27. A formulation as claimed in any one of claims 12 to 26 which is substantially free of mannitol.
28. A pharmaceutical formulation adapted for reconstitution as a liquid aqueous suspension comprising amoxycillin trihydrate and potassium clavulanate and which, when reconstituted, comprises amoxycillin in an amount $200 \pm 10\%$ and clavulanic acid in an amount $28.5 \pm 10\%$ or amoxycillin in an amount $400 \pm 10\%$ and clavulanic acid in an amount $57 \pm 10\%$ mg/5ml of liquid aqueous suspension.
29. A pharmaceutical formulation having a composition within $\pm 10\%$ of the formulae listed below, expressed as mg/5ml dose of reconstituted aqueous suspension:

Ingredient	mg/5ml	mg/5ml
amoxycillin trihydrate	408.0	204.0
potassium clavulanate	61.56	30.78
xanthan gum	12.5	12.5
colloidal silica	25.0	25.0
succinic acid	0.84	0.84
orange flavour	15.0	15.0
orange flavour	11.25	11.25
golden syrup flavour	23.75	23.75
aspartame	12.5	12.5
hydroxypropylmethylcellulose	79.65	79.65
silicon dioxide	to 885.5	to 537.5.

5 30. A pharmaceutical formulation as claimed in any one of claims 12 to 28 for use in therapy.

10 31. A process for manufacturing a formulation according to any one of claims 12 to 29 comprising the step of mixing dry powdered or granulated ingredients for loading into a suitable container.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/01881

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/43

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.INT.MED.RES., vol. 17, no. 2, 1989, pages 168-171, XP002010124 RUBERTO,U., ET AL.: "Amoxycillin and clavulanic acid in the treatment of urinary tract infections in children" see abstract see page 169, left-hand column, paragraph 3 --- -/--	1-11,28, 30

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

5 August 1996

Date of mailing of the international search report

21.08.96

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 96/01881

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CAN.MED.ASSOC.J., vol. 142, no. 2, 15 January 1990, pages 115-118, XP002010125 FELDMANN,W.,ET AL.: "Twice-daily antibiotics in the treatment of acute otitis media: trimethoprim-sulfamethoxazole versus amoxicillin-clavulanate" see abstract see page 116, left-hand column, paragraph 3 see page 116, right-hand column, last paragraph ---	1-11,28, 30
X	EUR.J.CLIN.MICROBIOL.INFECT.DIS., vol. 12, no. 5, May 1993, pages 319-324, XP002010126 JACOBSON,S., ET AL.: "Evaluation of amoxicillin clavulanate twice daily versus thrice daily in the treatment of otitis media in children" see abstract see page 319, left-hand column, line 1 - page 320, left-hand column, line 5 see page 320, left-hand column, paragraph 5 see page 320, left-hand column, last paragraph see page 323, left-hand column, paragraph 4 ---	1-11,28, 30
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